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13. ABSTRACT (Maximum 200 words)

During the course of this grant, we have made further progress on our optimization approach for protein structure prediction. This includes development of a preconditioned limited-memory quasi-Newton method, which should have broader applicability. We have also developed and analyzed a method for constrained optimization that uses a linear programming subproblem as an active set predictor. In our work on tensor methods we have developed a tensor method for large-scale nonlinear systems of equations using a Krylov iteration to compute the step.

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FINAL REPORT for

Army Research Office Grant DAAD19-02-1-0407
Developing and Understanding Methods for
Large-Scale Nonlinear Optimization

September 1, 2002 - December 31, 2005

Principal Investigator: Richard H. Byrd
Co-Principal Investigator: Robert B. Schnabel

1. Statement of the Problem Studied

This research supported by this grant involves development and study of algorithms for the numerical solution of large-scale nonlinear optimization problems. Optimization problems constitute an important class of mathematical problems whose computer solution is desired by scientists and engineers. The need to solve such problems arises in a huge variety of computer simulations and data analyses, with examples including optimal design of aircraft and spacecraft for low cost or high efficiency, optimal control of chemical processes, and calculation of the native states of biological molecules. In recent years, as computer power has increased, the feasibility of investigating optimal designs has increased, and along with this the need for improved optimization methods has grown. This requires fundamental research in optimization algorithms, especially for classes of large-scale problems.

In general, research in optimization algorithms has two strategic branches. One type of research focusses on broad purpose algorithms that can be ultimately incorporated into general purpose algorithms that can solve most problems in some class. Some applications, however, generate problems that require special purpose algorithms that are too difficult for such general methods and require development of algorithms that are tailored to that application. The research funded by the grant was in areas of both types. We worked on successive linear-quadratic programming algorithms for large-scale constrained optimization, and on tensor methods for fast solution of singular problems. Much of our effort was on the application of optimization to problems in molecular chemistry including prediction of protein structure by potential energy minimization.

One of the main emphases of this research program in recent years has been the development of global optimization methods for the solution of large molecular configuration problems. The objective of this research is to develop methods that are reliably capable of solving difficult, large nonlinear global optimization problems. Our current work is investigating methods to find the native configurations of proteins and polymers. This is a problem of great importance in science; it includes the well-known protein folding problem as well as the investigation of polymers that are used to make new materials. The resultant optimization problems are very difficult because they have extremely large numbers of local minimizers that have similar function values. In addition, some of the techniques developed in this effort have turned out to be of more general applicability.

Another main focus of our research is the development of new algorithms for large-scale unconstrained and constrained optimization problems, including limited-memory methods for problems with

many thousands of variables, and interior point methods for nonlinearly constrained problems. We were particularly interested in methods such as sucessive linear-quadratic programming that are capable of making good use of a woarm start. We are also investigating theoretical convergence issues for optimization algorithms that have practical consequences in how problems are formulated, and new approaches to one of the key numerical linear algebra subproblems that is particular to optimization algorithms.

2. Summary of the Most Important Results

A major focus in this grant has been the development and testing of techniques for solving global optimization problems for determining the structure of proteins and polymers. The problem is to find the lowest energy configuration of a protein or other polymer. This problem is a global optimization problem because it has a huge number of local minimizers. In addition, locating the lowest (global) minimizer is very difficult. For proteins, the solution of this problem would represent a solution to the well-known protein-folding problem.

In previous years, we have developed a stochastic/perturbation approach for solving global optimization problems from molecular chemistry. There are four keys to this approach. The first is a large scale global optimization methodology that performs small-scale global optimizations with only a small number of parameters variable and the remaining parameters temporarily fixed, followed by local minimizations with all parameters varying, at each stage of the global optimization procedure. The second is the incorporation of a new, efficient approach towards smoothing the objective function in the global optimization framework. Initially these have been the backbone of the approach. More recently two other aspects have become key to doing work on realistic protein targets. One of these is the incorporation of predictions from secondary structure prediction methods in the initial phase of our algorithm, to produce starting configurations with reasonably good secondary structure. The final one is work with our chemistry partners to use the mismatch between simulation and experimental evidence to continue to refine the mathematical energy model upon which our global optimization approach relies.

By now, we have evolved our approach to be able to handle proteins with arbitrary structure and size. The crux of this issue, for us and other groups doing related research, is the ability to handle beta-sheets. Beta-sheets are the other main type of secondary structure in proteins. However they are far less local than alpha-helices. While alpha-helices are continuous, beta-sheets are formed by contiguous strands that can be arbitrarily far apart. Secondary structure prediction programs can predict the strands with good accuracy, but they do not predict which strands are bonded together, nor the parallel or anti-parallel orientation of those bonds. Our progress in this area was tested in the fifth Critical Assessment of Techniques for Protein Structure Prediction (CASP5) competition, which started in summer 2002 with results presented in December 2002. Our performance in the "new fold" category, for which our method is appropriate ranked approximately 18th among the 190 participating groups.

We have also made significant progress in improving the local minimization phase of our global minimization algorithm. In a run of this method, many unconstrained local optimization problems must be solved, for which we have mainly been using the limited memory quasi-Newton method L-BFGS. In this period we have focussed on improving the efficiency of this local optimization phase by developing a local method that applies a preconditioner to the the limited memory BFGS method. The preconditioner consists of an approximation to part of Hessian matrix of the objective function. We have found good ways of modifying the preconditioner to make it positive definite. The effect of this preconditioning is to

reduce the number of iterations sufficiently to more than compensate for the cost of computing the preconditioner. Thus we have been able to reduce the total time of a local minimization by a factor of 5 to 6. We expect this improvement to have a significant effect on the global optimization procedure. This work has been described in a paper submitted to *SIAM Journal on Optimization*.

We have continued our work on methods for large-scale nonlinearly constrained optimization with Jorge Nocedal at Northwestern University. Our efforts to develop a method based on using successive solution of linear programs as a predictor of active sets has been fairly successful and a paper describing it has been published by Mathematical Programming. Although this method is not necessarily more powerful than primal-dual interior point methods, it should be much more capable of making good use of a warm starting point. This is important in problems with variable sized discretizations and in branch and bound approaches. We have been able to establish some new global convergence results for this method which have been described in a paper published in *SIAM Journal on Optimization*. We have also developed a software implementation of this method, which has been distributed as part of the KNITRO package.

We also continued work on tensor methods for solving large-scale systems of nonlinear equations. We have developed a "tensor-Krylov" method that solves a local tensor model to within a specified relative tolerance using the techniques associated with linear Krylov subspace methods and, in particular, the Generalized Minimum Residual method (GMRES). Our tensor-Krylov method works better than Newton-GMRES on problems that have an ill-conditioned or singular Jacobian at the problem root. These types of problems are encountered in scientific and engineering applications that, for example, exhibit shocks. This work is main part of the doctoral dissertation of Brett Bader who was supported on this grant and is now at Sandia National Laboratories. Papers on this work have been published in SIAM Journal on Scientific Computing and SIAM Journal on Numerical Analysis, and one more has been submitted.

3. List of All Publications and Technical Reports

"Published in peer-reviewed journals"

E. Eskow, B. Bader, R. Byrd, S. Crivelli, T. Head-Gordon, V. Lamberti and R. Schnabel, "An optimization approach to the problem of protein structure prediction," *Mathematical Programming 101*, pp. 497-514 (2004),

R. Byrd, N. Gould, J. Nocedal, and R. Waltz, "An algorithm for nonlinear optimization using linear programming and equality constrained subproblems," *Mathematical Programming 100,* pp. 27-48 (2004).

R. Byrd, M. Marazzi and J. Nocedal, "On the convergence of Newton iterations to non-stationary points," *Mathematical Programming 99,* (2004) pp. 127-148

R. Byrd, J. Nocedal and R. Waltz, "Feasible Interior Methods Using Slacks for Nonlinear Optimization," *Computational Optimization and Applications, 26(1),* (2003) pp. 35-61

R. Byrd, N. Gould, J. Nocedal, and R. Waltz. "On the convergence of successive linear-quadratic

programming algorithms," *SIAM Journal on Optimization 16,* pp. 471-489, (2005).

E. Prudencio, R. Byrd, and X.-C. Cai, "Parallel full space SQP Lagrange-Newton-Krylov-Schwarz algorithms for PDE-constrained optimization problems, *SIAM J. Sci. Comput. 27* (2006), pp. 1305-1328.

B. Bader and R. Schnabel, "Curvilinear linesearch for tensor methods", *SIAM Journal on Scientific Computing 25,* 2003, pp. 2004-2022.

B. Bader "Tensor-Krylov Methods for Solving Large-Scale Systems of Nonlinear Equations" *SIAM J. Num. Anal. 43,* (2005), pp. 13211347.

Published in conference proceedings

Jinhui Ding, Elizabeth Eskow, Nelson Max, Silvia Crivelli, "Protein Structure Prediction Using Physical-Based Global Optimization and Knowledge-Guided Fragment Packing," csbw, pp. 211-212, 2005 IEEE Computational Systems Bioinformatics Conference - Workshops (CSBW'05), 2005

E. Prudencio, R. Byrd, and X.-C. Cai, Domain decomposition methods for PDE constrained optimization problems, M. Dayde, J. Dongarra, V. Hernandez, and J. Palma, edt., *Lecture Notes in Computer Science,* Vol. 3402, Springer, 2005.

R. Byrd, J. Nocedal, and R. Waltz, "KNITRO: An Integrated Package for Nonlinear Optimization", in *Large-Scale Nonlinear Optimization* G. Di Pillo and M. Roma, eds., Springer 2006.

Submitted but not yet accepted:

L. Jiang, R.H. Byrd, E. Eskow, and R.B. Schnabel, "A preconditioned L-BFGS algorithm with application to molecular energy minimization," submitted to *SIAM Journal on Optimization.*

B. Bader and R. Schnabel, "On the performance of tensor methods for solving ill-conditioned problems", submitted to *SIAM Journal on Scientific Computing.*

4. Participating Scientific Personnel

Betty Eskow, Professional Research Assistant

Brett Bader, doctoral student, Ph.D. 2003.

Lianjun Jiang, doctoral student (doctorate expected 2006).